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New alkyl-phenylimino-imidazolidine derivatives
for treating urinary incontinence

The present invention relates to m-alkyl-phenylimino-imidazolidine derivatives with a new pattern of substituents at the phenyl ring and their use in preparing pharmaceutical compositions, particularly for treating urinary incontinence.

Prior art

The compounds described within the scope of the present invention belong to the category of m-alkyl-phenylimino-imidazolidines. Similar compounds are known from the prior art.

WO 96/32939, to which reference is hereby made in its entirety, discloses phenylimino-imidazoles. These include those compounds wherein the phenyl ring contains, *inter alia*, amino, amido, imido, halo, heteroaryl, cycloalkyl and alkyl substituents. The compounds described therein count as alpha-1L-agonists and may advantageously be used in this capacity for the treatment of urinary incontinence.

By incontinence is meant an involuntary release of urine, i.e. weakness of the bladder. The various manifestations of urinary incontinence include urge incontinence, reflex incontinence, overflow incontinence and stress incontinence. Among the most common forms of urinary incontinence is stress incontinence. Women, in particular, are affected by this after more or less difficult childbirth. The reason for this is that pregnancy and labour easily lead to a weakening of the pelvic floor. Other causes of incontinence may lie, for example, in damage to the nerves of the pelvic floor, a congenitally short urethra or damage to the sphincter muscle.

It is beneficial to use alpha-1L-agonists in the treatment of urinary incontinence, as they act selectively on the adrenoreceptors of the bladder and thus have a crucial effect on the tonicity of the urethra, without significantly affecting the cardiac circulatory system.

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For some time, the possibility of using imidazole derivatives to treat incontinence has been discussed in the prior art. Surprisingly, opinions have been expressed indicating that many imidazole derivatives can counteract weakness of the bladder, while other authors have observed apparently the reverse effect, namely that these substances can give relief in occlusion of the bladder. Still other authors report that these same substances would have no effect at all on bladder function.

Thus, it is reported that alpha 2 agonists such as clonidine would have a positive effect on nocturnal incontinence (Urology, 43 (3) (1994) 324 – 327). On the other hand, the contrary observation has been made with regard to clonidine, that this substance could even promote incontinence (Clin. Biol. Res. 78 (1981) 101 – 103). A similar observation is expressed in Jpn. J. Pharmacol. 58 (4) (1992) 339 – 346. The authors have found that clonidine does not have a clear effect on bladder function, but that phenyl-ethanol-amines, such as the phenylephrines, midodrine or ST 1059 which resemble adrenaline, all of which are alpha 1 agonists, do have an effect. EP-A-0 416 841 relates to the effect of alpha agonists on bladder function. It states that alpha 1 adrenoceptor-blocking substances can be used to treat occlusion of the bladder. The observations according to US-A-4 226 773 point in this direction. According to this specification, pyrazolyl-imino-imidazole derivatives can be used to promote the release of urine. Other alpha 1 adrenergic imidazoles such as thiophene-pyrroles, for example, may be used to treat urinary incontinence (EP-A-0 599 697).

These different observations from the prior art lead one to conclude that it has not hitherto been possible to predict the effect of imidazole derivatives on bladder function.

Description of the invention

Compounds which can be used to treat urinary incontinence not only have to be sufficiently effective but should also have as few side effects as possible. In other words, they should act as selectively as possible on the bladder alone. The unwanted side effects include, *inter alia*, a negative effect on the cardiac circulatory system. The bioavailability of the substances and their metabolism are of particular importance to particularly effective treatment of urinary incontinence. The

bioavailability should be as high as possible and the metabolism should be such that, on the one hand, the substances are not broken down too quickly and, on the other hand, no toxic or other compounds with pharmacological properties which are undesirable in this context are formed.

Therefore, one of the aims of the present invention is to find new 1L-agonists from the category of phenylimino-imidazolidines which act selectively on the bladder without substantially affecting the cardiac circulatory system and have favourable properties with regard to bioavailability or metabolism.

Surprisingly, it has been found that the m-alkyl-phenylimini-imidazolidines according to the invention achieve the aims of the present invention and are therefore suitable for treating urinary incontinence.

Alkyl-phenylimino-imidazolidines with branched alkyl groups are known in principle from the prior art.

Thus, for example, WO 92/21349 discloses a number of phenylimini-imidazolidine derivatives for ophthalmological use. DE 1929950 describes *inter alia* 2'-bromo-5'-chloro-4'-tert.butyl-phenylimini-2-imidazolidine and DE 0116768 describes 2,6-dichloro-4'-tert.butyl-phenyliminoimidazolidine.

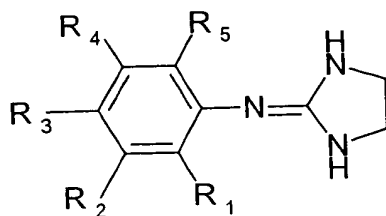
EP 0035393 also relates to alkylphenylimino-imidazolidines, albeit not for use in human medicine but for the production of hens' eggs.

Detailed description of the invention

The alkyl-phenylimino-2-imidazolidine derivatives according to the invention are characterised in that there is a branched C₃-C₆-alkyl group, such as e.g. isopropyl, isobutyl, tert. butyl, isopentyl or neopentyl, in at least one of the two possible *meta* positions to the imino group. Preferably, there is an isopropyl and/or a tert. butyl group. The preferred compounds according to the invention are described by general formula I:

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Formula I:



wherein

R₁ or R₅ independently of one another denote H, F, Cl, Br, CF₃, Me or OMe

R₂, R₄ independently of one another each denote H, iPr, tert.Bu, F, Cl, Br, CF₃ or Me,

while at least one of the groups R₂ or R₄ is iPr or tert.Bu

R₃ is H, F, Cl, Br, CF₃, Me.

Me denotes methyl, CF₃ denotes trifluoromethyl, iPr denotes isopropyl, H denotes hydrogen, F denotes fluorine, Cl denotes chlorine, Br denotes bromine and tert.Bu denotes tertiary butyl.

If R₅ is OMe, compounds wherein R₂ is tert.Bu are preferred.

Of the compounds specified, the preferred ones are those wherein

R₁ or R₅ independently of one another denote H, F, Cl, Br, CF₃, Me or OMe

R₂, R₄ independently of one another each denote H, iPr, tert.Bu, Me,

while at least one of the groups R₂ or R₄ is iPr or tert.Bu

R₃ is H, F, Cl, Br, Me.

Of these, particularly preferred compounds are those wherein

R₁ is H, Cl, Br, Me,

R₂ is iPr, tert.Bu,

R₃ is H, Br, Cl,

R₄ is H and

R₅ is H, Cl, Br, OMe.

Most preferred are compounds wherein

R_1 is H, Me

R_2 is iPr, tert.Bu,

R_3 is H, Cl; Br,

R_4 is H and

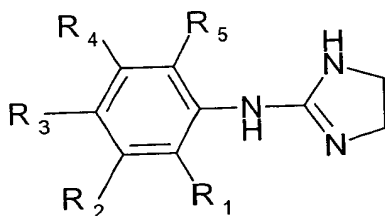
R_5 is H, Cl, OMe.

In every case R_2 is preferably iPr, tert.Bu, while R_4 is preferably H.

Again, in every case, R_1 is preferably different from OMe.

The compounds represented by formula I may be in tautomeric equilibrium with the alkyl-anilino-2-imidazoline derivatives of formula II:

Formula II



wherein the definitions of the groups R_1 , R_2 , R_3 , R_4 and R_5 are identical to those of the abovementioned compounds of formula I including all the preferences listed. Therefore, the present invention also relates to the compounds coming under general formula II in which the groups R_1 , R_2 , R_3 , R_4 and R_5 fall within the scope of the definition given under formula I. The same is true of the preferred ranges mentioned under formula I.

The compounds which come under the scope of the definitions of formulae I and II are equally preferred but independently of one another.

Some alkyl-phen-1'-yl-2-imidazolidines will now be listed by way of example of all the compounds which fall under general formula I or II. With regard to the nomenclature

used in the present invention it should be pointed out that the carbon atom of the phenyl ring which is linked to the 2-position of the imidazolidine via the imino group is designated 1' throughout and the branched alkyl substituent in the *meta* position is designated 3'.

It should be expressly pointed out that the corresponding tautomers according to general formula II are also included in the invention and therefore chemical names which indicate the structure of formula I also include the corresponding alkyl-anilino-2-imidazolidine derivatives according to formula II and *vice versa*.

3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 1, which is preferably in the form of the free base

3'-tert. butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 2, which is preferably in the form of the free base

6'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 3, which is preferably in the form of the free base

4'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 4, which is preferably in the form of the free base

6'-bromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 5,

6'-bromo-3'-tert.butyl-phen-1'-yl-2-iminoimidazolidine 6,

4'-bromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 7,

5',6'-dibromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 8,

5',6'-dichloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 9,

2',6'-dichloro-3'-isopropyl-phen-1'-yl-2-iminoimidazolidine 10,

4',6'-dibromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 11,

4',6'-dichloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 12,

2',5'-dichloro-3'-isopropyl-phen-1'-yl-2-iminoimidazolidine 13,

2',6'-dibromo-3'-isopropyl-phen-1'-yl-2-iminoimidazolidine 14,

6'-bromo-5'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 15,

6'-bromo-4'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 16,

6'-bromo-2'-chloro-3'-isopropyl-phen-1'-yl-2-iminoimidazolidine 17,

5'-trifluoromethyl-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 18.

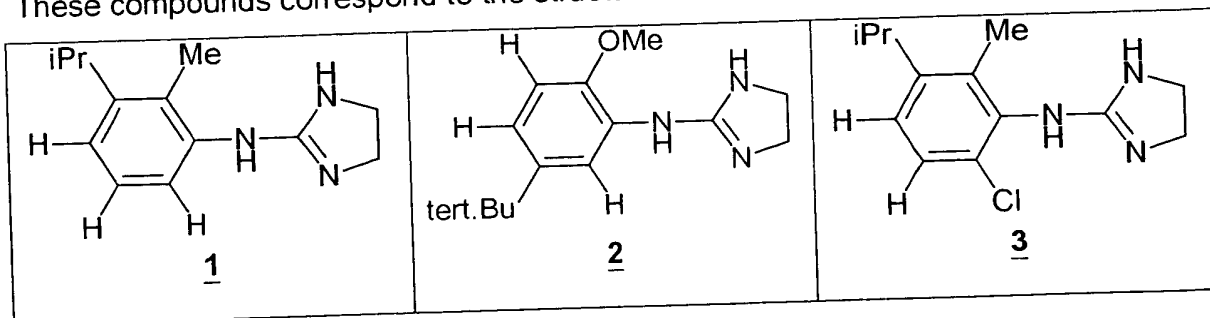
4',5'-dichloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 19,

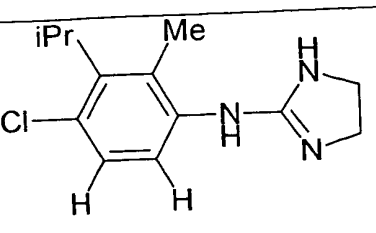
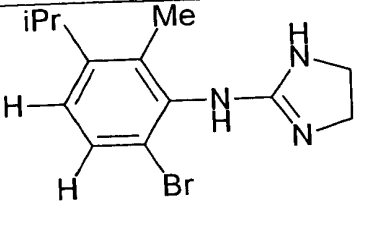
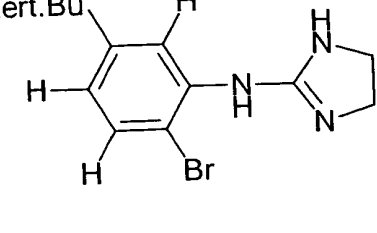
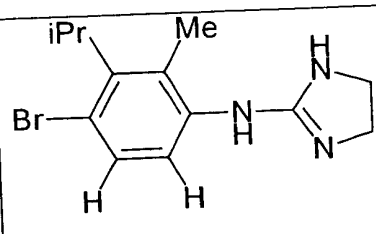
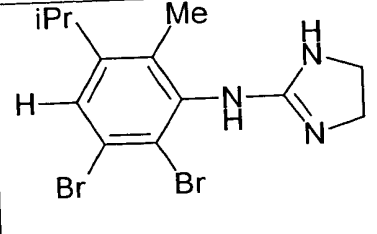
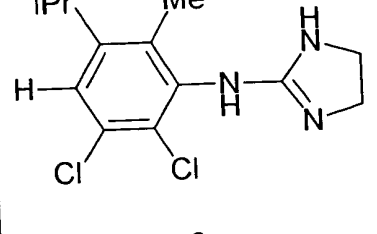
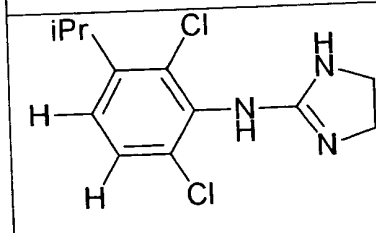
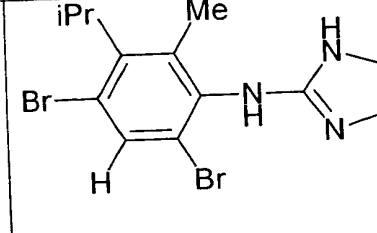
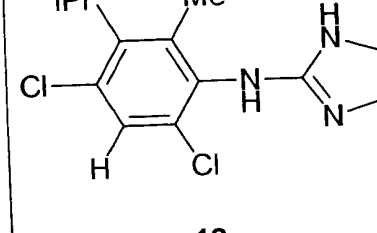
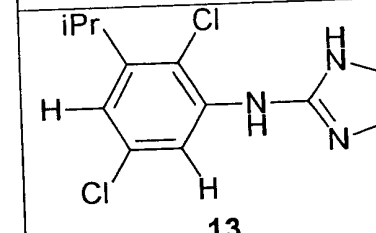
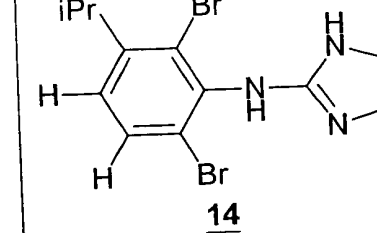
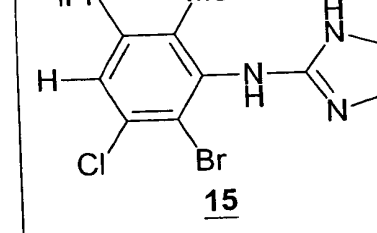
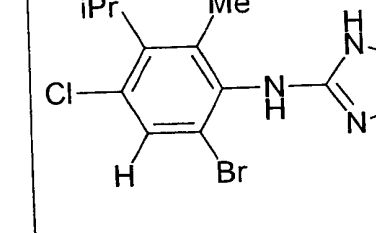
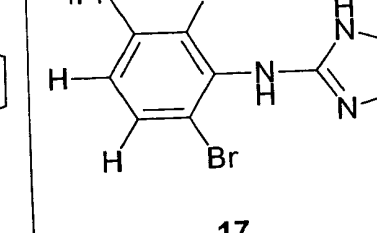
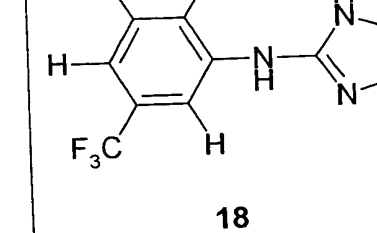
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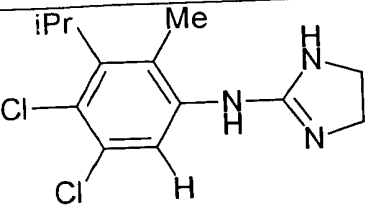
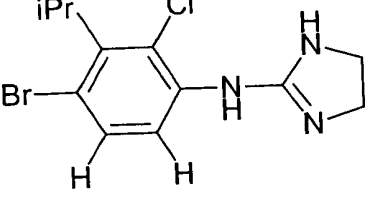
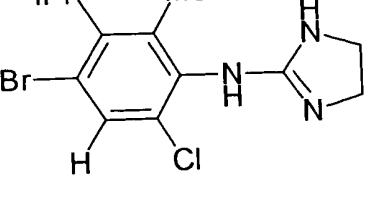
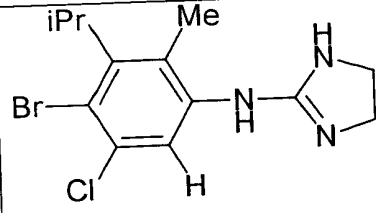
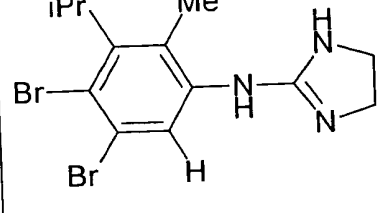
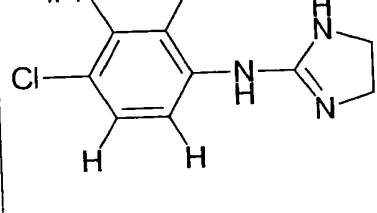
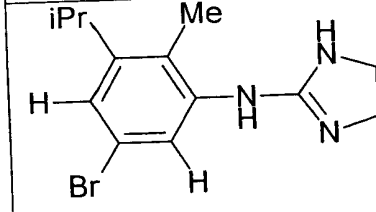
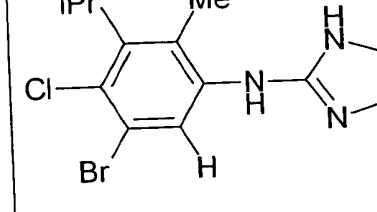
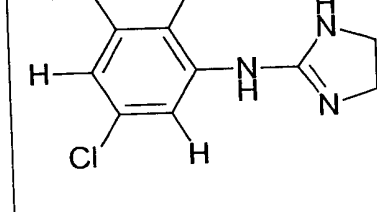
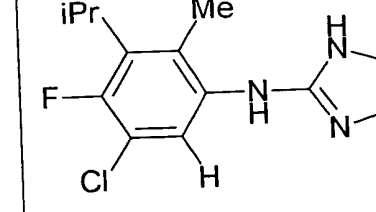
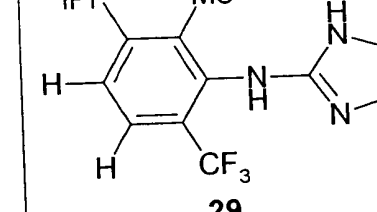
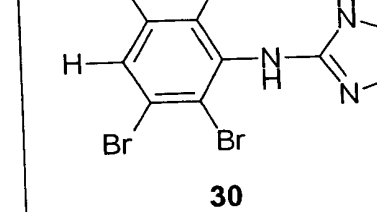
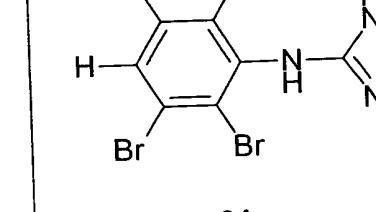
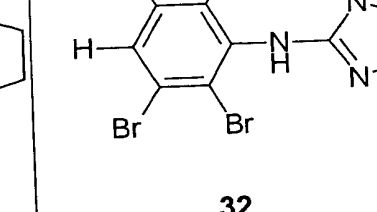
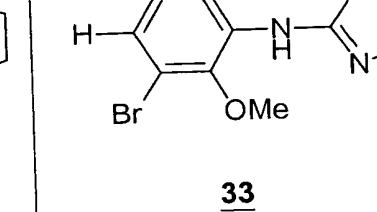
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4'-bromo-5'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 22,
4',5'-dibromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 23,
2',4'-dichloro-3'-isopropyl-phen-1'-yl-2-iminoimidazolidine 24,
5'-bromo-2'-methyl-3'-isopropyl-phen-1'-yl-2-iminoimidazolidine 25,
5'-bromo-4'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 26,
5'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 27,
5'-chloro-4'-fluoro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 28,
6'-trifluoromethyl-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 29,
2',5',6'-tribromo-3'-tert.butyl-phen-1'-yl-2-iminoimidazolidine 30,
5',6'-dibromo-3'-tert.butyl-phen-1'-yl-2-iminoimidazolidine 31,
5',6'-dibromo-3'-tert.butyl 2'-chloro-phen-1'-yl-2-iminoimidazolidine 32,
2',5'-dibromo-3'-tert.butyl 6'-methoxy-phen-1'-yl-2-iminoimidazolidine 33,
2',5'-dichloro-3'-tert.butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 34,
2',6'-dibromo-3'-tert.butyl 5'-chloro-phen-1'-yl-2-iminoimidazolidine 35,
2',6'-dibromo-3'-tert.butyl-phen-1'-yl-2-iminoimidazolidine 36,
6'-bromo-3'-tert.butyl-2',5'-dichloro-phen-1'-yl-2-iminoimidazolidine 37,
6'-bromo-3'-tert.butyl-5'-chloro-phen-1'-yl-2-iminoimidazolidine 38,
2'-bromo-3'-tert.butyl-5'-chloro-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 39,
2'-bromo-3'-tert.butyl-6'-chloro-phen-1'-yl-2-iminoimidazolidine 40,
2'-bromo-3'-tert.butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 41,
2'-chloro-3'-tert.butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 42,
5'-bromo-3'-tert.butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 43,
5'-chloro-3'-tert.butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 44,
5'-bromo-3'-tert.butyl-2'-chloro-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 45.

These compounds correspond to the structures:

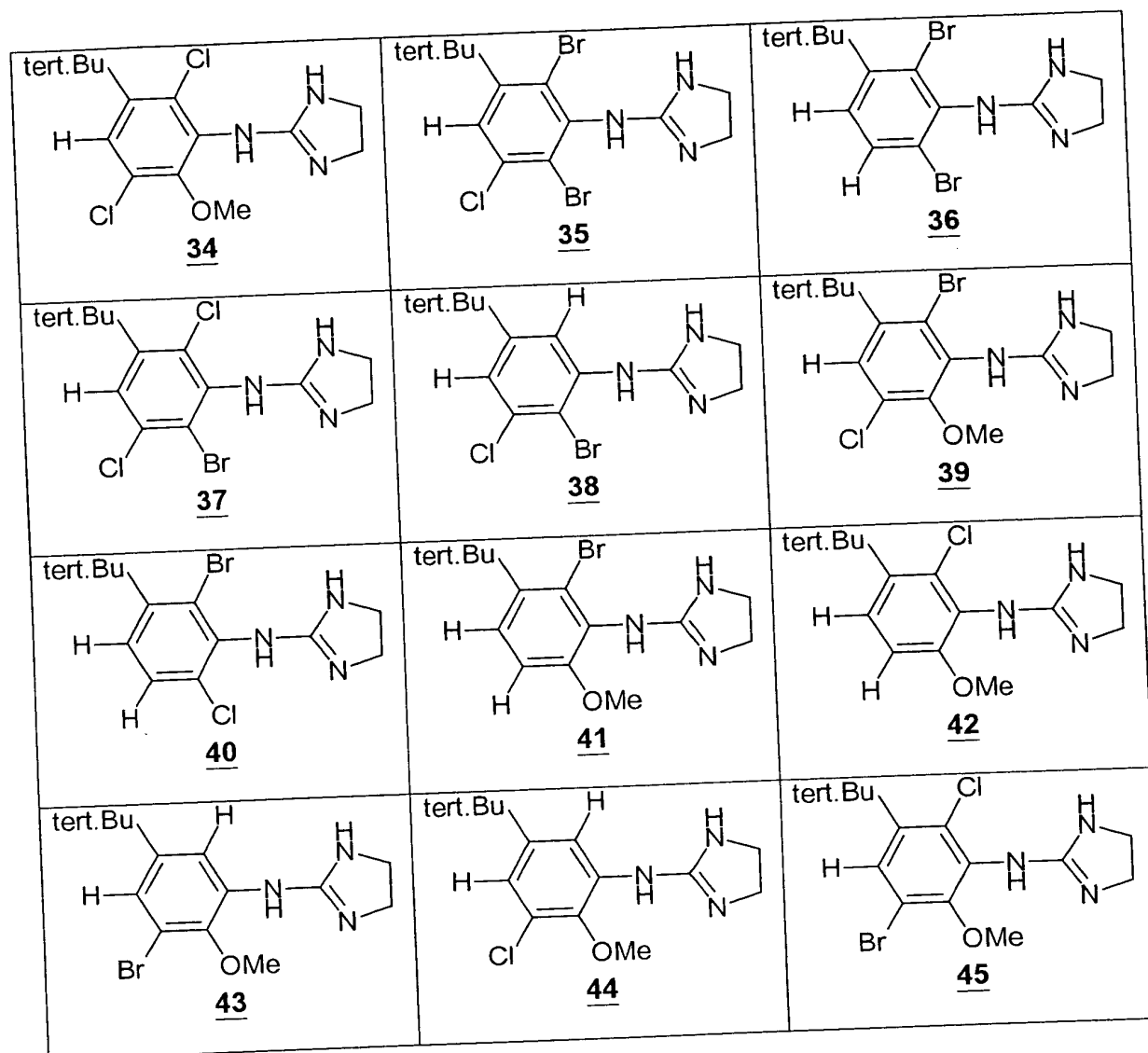


 <u>4</u>	 <u>5</u>	 <u>6</u>
 <u>7</u>	 <u>8</u>	 <u>9</u>
 <u>10</u>	 <u>11</u>	 <u>12</u>
 <u>13</u>	 <u>14</u>	 <u>15</u>
 <u>16</u>	 <u>17</u>	 <u>18</u>

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 <u>19</u>	 <u>20</u>	 <u>21</u>
 <u>22</u>	 <u>23</u>	 <u>24</u>
 <u>25</u>	 <u>26</u>	 <u>27</u>
 <u>28</u>	 <u>29</u>	 <u>30</u>
 <u>31</u>	 <u>32</u>	 <u>33</u>

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Of these compounds, the following are preferred:

- 3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine **1**,
- 3'-tert. butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine **2**,
- 6'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine **3**,
- 4'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine **4**,
- 6'-bromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine **5**,
- 6'-bromo-3'-tert.butyl-phen-1'-yl-2-iminoimidazolidine **6**,
- 4'-bromo-3'-isopropyl-2'-methyl-1'-phen-yl-2-iminoimidazolidine **7**.

Of these compounds, the following are particularly preferred :

- 3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine **1**,

3'-tert. butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 2,
6'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 3,
4'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 4,
4'-bromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 7.

Of these compounds, the following are most preferred:

3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 1,
3'-tert. butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 2,
6'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 3,
4'-bromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 7.

The following are also preferred compounds:

4',5'-dichloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 19,
2'-chloro-3'-tert.butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 42,
5'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 27,

Examples 1, 3, 4, 5 and 7 to 29 relate to structures with an isopropyl group in the meta position, Examples 2, 6 and 30 to 45 relate to structures with a tert.-butyl group in the meta position, which in turn form preferred groups.

Not only the abovementioned compounds but also the pharmaceutically acceptable acid addition salts thereof are claimed in the present invention.

Suitable acids for this purpose may be either inorganic or organic by nature.

Examples of suitable acids include:

hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, citric acid, lactic acid, acetic acid, propionic acid, malic acid, succinic acid, amino acid, particularly glutamino acid or aspartic acid, carbohydrate acids and acids derived from carbohydrates. These salts may be important both for galenic preparation, they may increase the stability, especially the long-term stability of the compound and/or lead to an increase in the bioavailability. Hydrochloride salts are preferred, either the monohydrochlorides or dihydrochlorides, depending on the compound. The same is true of the preferred compounds.

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As already indicated hereinbefore, the abovementioned compounds according to the invention are characterised not only by their efficacy but in particular by their pharmacological properties with regard to bioavailability and/or metabolism. It goes without saying that the most preferred compounds are those which exhibit high efficacy and bioavailability with minimal metabolic breakdown. Another significant feature for choosing particularly suitable compounds for the treatment of urinary incontinence is the selectivity with which the compound in question acts on bladder function without seriously affecting other body functions, particularly the cardiac circulatory system.

Apart from the abovementioned compounds and the pharmacologically acceptable acid addition salts thereof, the present invention also includes the use thereof for preparing medicaments and pharmaceutical preparations. These preparations include all formulations which are suitable for medical use. These include, for example, solutions, suspensions, aerosols, powders, plain and coated tablets, suppositories, creams, etc.

The compounds according to the invention, the pharmacologically acceptable acid addition salts thereof and/or pharmaceutical preparations containing them can be used medically for the treatment of complaints, particularly bladder complaints, especially urinary incontinence. The compounds according to the invention are most preferably used to treat stress incontinence.

In another aspect the present invention relates to processes for preparing the abovementioned compounds, the pharmacologically acceptable acid addition salts thereof and/or pharmaceutical preparations, as well as the use of the compound described for the preparation of other pharmacologically active derivatives thereof.

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Examples

1. Bioavailability

To determine the bioavailability the test substances were administered orally to a group of 8 male fasted rats. As a control, animals in an identical second group were given the test substances intravenously. At specified times after administration (10 minutes, 30 minutes, 1 hour, 2 hours and 4 hours, and additionally 6 hours in the case of the animals in the oral group) 1 ml blood samples were taken from the animals in both groups. The blood samples taken in each group were mixed together (8 ml). The content of the test substances in the blood for the appropriate time was determined from the plasma after further working up by HPLC (High Performance Liquid Chromatography) using standard methods and correlated for the two groups.

Results

Compound	Bioavailability in %
<u>2</u>	34
<u>3</u>	8
<u>7</u>	53

2. Metabolism

To determine the metabolism the enzyme CYP2D6 was allowed to act on the test substances. After 30 minutes a check was made to see how much of the test substance put in had been degraded by the enzyme.

The decomposition under the effect of the enzyme HLM / 60 minutes was tested analogously.

Compound	% substrate breakdown after 30 minutes incubation with CYP2D6	substrate breakdown after 60 minutes incubation with HLM
<u>1</u>	18.2	13.5
<u>2</u>	0.7	2.7
<u>3</u>	6.1	11.7
<u>4</u>	7.6	5.5
<u>5</u>	8.7	7.5
<u>6</u>	3.0	2.8
<u>7</u>	5.0	

3. Efficacy and selectivity

The efficacy and selectivity of the compounds is determined as follows:

Compound	activity in the dog	activity on human urethra	selectivity in the dog
<u>1</u>	78	11	0.7
<u>2</u>	71	30	0.6
<u>3</u>	70	41	0.7
<u>4</u>	59		0.5
<u>5</u>	34		0.4
<u>6</u>	28		
<u>7</u>	70	21	0.7

Maximum contraction in the dog and activity on human urethra are percentages of contraction compared with noradrenaline.

Selectivity in the dog: percentage contraction of the dog's femoral artery at 10^{-5} M – percentage contraction of the carotid artery in the dog at 10^{-5} M.

4. Preparation

Examples of preparation

3'-Isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 1

Step 1

10 g of 2-methyl-3-nitrobenzoic acid are placed in a mixture of 100 ml of methylene chloride and 1 ml of dimethylformamide. 8.9 g of thionyl chloride are slowly added dropwise and the mixture is refluxed. After 6 hours the solvent is evaporated down under reduced pressure.

11.5 g of 2-methyl-3-nitro-benzoic acid chloride are obtained as an oil.

Step 2

11.7 g of diethyl malonate, 3.5 g of anhydrous magnesium dichloride and 14.7 g of triethylamine are added successively to 70 ml of ethyl acetate and stirred for 0.5 hours at ambient temperature. After cooling to 10°C, 11.5 g of 2-methyl-3-nitro-benzoic acid chloride are slowly added dropwise. The mixture is then stirred at 60°C. After 3 hours the methylene chloride is distilled off under reduced pressure. The residue is carefully mixed with 50 ml of water and adjusted to pH1 with 4N HCl solution. The reaction mixture is extracted 3 times with 3x100 ml ethyl acetate. The combined organic phases are washed once again with water, dried and evaporated down under reduced pressure. The oily residue is purified by chromatography (silica gel, eluant: cyclohexane/ethyl acetate (3/1).

18.6 g of diethyl 2-(2-methyl-3-nitro-benzoyl)-malonate are obtained as a yellow oil.

Step 3

18.6 g of diethyl 2-(2-methyl-3-nitro-benzoyl)-malonate are placed in 15 ml of concentrated acetic acid. 3.5 ml of distilled water and 3.5 ml of concentrated H₂SO₄ are slowly added. The mixture is refluxed. After 4 hours it is cooled, diluted with 50 ml of water, made alkaline with 30% NaOH solution while cooling with ice and extracted with 3x100 ml of ethyl acetate. The combined organic phases are dried and evaporated down under reduced pressure.

8.3 g of 1-(2-methyl-3-nitro-phenyl)-ethanone are obtained as light yellow crystals.

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Step 4

5 g of 1-(2-methyl-3-nitro-phenyl)-ethanone are dissolved in about 50 ml of methanol and hydrogenated at 20°C and 5 bar with hydrogen using Raney nickel as catalyst. The catalyst is separated off and the filtrate is evaporated down under reduced pressure. The product is purified by chromatography (silica gel, eluant: cyclohexane/ethyl acetate (3/1)).

3.5 g of 1-(2-methyl-3-amino-phenyl)-ethanone are obtained as light yellow crystals.

Step 5

0.9 g of 60% sodium hydride oil dispersion are placed in 11.5 ml of DMSO. The suspension is stirred at 80°C until no further development of gas can be seen (about 30 min.). It is cooled to 10°C and then a solution of 3.5 g of 1-(2-methyl-3-amino-phenyl)-ethanone and 1 ml of DMSO is slowly added dropwise. The reaction temperature rises to 45°C. After 10 minutes a solution of 8.2 g of methyltriphenylphosphonium bromide in 23 ml of DMSO is slowly added dropwise at about 30°C. The mixture is stirred for another 4 hours without any external heat supply (RT) and then combined with 100 ml of methylene chloride and 100 ml of water. The aqueous phase is separated off and extracted twice more with 75 ml of methylene chloride. The combined organic phases are washed with water, dried and concentrated under reduced pressure. The product is purified by chromatography (silica gel, eluant: cyclohexane/ethyl acetate (3/1)).

3.4 g of 3-isopropenyl-2-methyl-aniline are obtained as a clear yellow oil.

Step 6

15.4 g of 3-isopropenyl-2-methyl-aniline are dissolved in about 150 ml of methanol and hydrogenated with hydrogen at 60°C and 12 bar using Raney nickel as catalyst. The catalyst is separated off and the filtrate is evaporated down under reduced pressure.

14.4 g of 3-isopropyl-2-methyl-aniline are obtained as a clear colourless oil.

Step 7

7.45 g of 3-isopropyl-2-methyl-aniline and 8.7 g of N-acetyl-methylmercaptoimidazolidine are refluxed for 3 hours in 100 ml of isopropanol. The solvent is distilled off under reduced pressure and the oily residue is refluxed in 100 ml of methanol.

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After 12 hours the solution is concentrated down to a small volume under reduced pressure, made alkaline with 30% NaOH solution while cooling with ice and extracted twice with ethyl acetate. The combined organic phases are dried and evaporated down under reduced pressure. The oily residue is dissolved in 55 ml of HCl solution (1N) and 55 ml of water. The solution formed is fractionally precipitated with NaOH solution (2N) at increasing pH and extracted with diethylether until it contains the desired substance. After it has been made alkaline with NaOH solution, a solid substance is precipitated. It is suction filtered, washed with water and dried. 6 g of 3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine are obtained as a white powder, melting point 133-135°C.

6'-bromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 5
and
4'-bromo-3'-isopropyl-2'-methyl-1'-phen-yl-2-iminoimidazolidine 7

Step 1

7.45 g of 3-isopropyl-2-methyl-aniline (Example 1, Step 6) are dissolved in 75 ml of dimethylformamide and cooled to 5°C. A solution of 8.9 g of N-bromo-succinimide and 50 ml of DMF is carefully added dropwise within 45 minutes. The mixture is stirred for 1 hour at 3-5°C. Then the solution is added to about 1 l of ice water and extracted three times with ethyl acetate. The combined organic phases are dried and evaporated down under reduced pressure. The two bromine isomers are isolated by chromatography (silica gel, eluant: toluene/acetone (9/1)).

1.87 g of 2'-bromo-5'-isopropyl-6'-methylaniline and 8 g of 4'-bromo-3'-isopropyl-2'-methylaniline are obtained as oils.

Step 2

2.28 g of a mixed fraction of 6'-bromo-3'-isopropyl-2'-methylaniline and 4'-bromo-3'-isopropyl-2'-methylaniline are dissolved in 45 ml of acetonitrile. 1.67 g of 2-N-acetylimidazolidin-2-one and 4.6 g of POCl₃ are added one after the other. The mixture is refluxed for 4 hours and then stirred at ambient temperature. After 12 hours the solvent is distilled off under reduced pressure. The residue is treated with 50 ml of ice water and extracted twice with ethyl acetate. The aqueous phase is. 0.5 g of a white solid is precipitated, which is suction filtered and dried (F1). The

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combined organic phases are evaporated down under reduced pressure. The residue is treated with water. The aqueous phase is filtered and again made alkaline with an NH_4OH solution while being cooled and extracted twice with ethyl acetate. The combined organic phases are dried and evaporated down under reduced pressure (F2 – 0.9 g).

F1 and F2 are refluxed together in 20 ml methanol. After 5 hours the solvent is distilled off under reduced pressure. The two bromine isomers are separated by chromatography (silica gel, eluant: methylene chloride/methanol/ammonia (9/1/1%)). 0.15 g of 6'-bromo-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine are obtained as a hygroscopic white powder.

0.45 g of 4'-bromo-3'-isopropyl-2'-methyl-1'-phen-yl-2-iminoimidazolidine are obtained as a white powder, melting point 178–181°C.

6'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 3

and

4'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 4

Step 1

7.45 g of 3-isopropyl-2-methyl-aniline are dissolved in 75 ml of dimethyl formamide. A solution of 6.7 g of N-chloro-succinimide in 50 ml of DMF is slowly added dropwise. The reaction is slightly exothermic. After one night at ambient temperature the solution is diluted with water and extracted with ethyl acetate. The combined organic phases are dried and evaporated down under reduced pressure. The two chlorine isomers are isolated by chromatography (silica gel, eluant: petroleum ether/ethyl acetate (95/5)).

2.16 g of 6'-chloro-3'-isopropyl-2'-methylaniline and 3.95 g of 4'-chloro-3'-isopropyl-2'-methylaniline are obtained in the form of oils.

Step 2

In the case of the 6'-chloro-3'-isopropyl-2'-methylaniline regioisomer, the iminoimidazolidine is prepared as for compound 1 – Step 7.

3.03 g of 6'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine (3) are obtained as a hygroscopic brown powder from 3.95 g of 6'-chloro-3'-isopropyl-2'-methylaniline.

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In the case of the 4'-chloro-3'-isopropyl-2'-methylaniline regioisomer, the iminoimidazolidine is prepared analogously to compounds 5 and 7 – Step 2. 1.45 g of 4'-chloro-3'-isopropyl-2'-methyl-phen-1'-yl-2-iminoimidazolidine 4 are obtained as a hygroscopic brown powder from 2.16 g of 4'-chloro-3'-isopropyl-2'-methylaniline.

3'-*tert*-Butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine 2

Step 1

2.04 g of potassium isothiocyanate are dissolved at 10°C in 60 ml of acetone. 2.38 ml of benzoylchloride are carefully added dropwise. The white suspension is refluxed for 10 minutes and cooled at 10°C. Then a solution of 40 ml of acetone and 3.63 ml of 5-*tert*-butyl-2-methoxyaniline is added. The solution is then refluxed. After 3 hours 100 ml of ice water are added and the mixture is extracted with 3x80 ml of ethyl acetate. The combined organic phases are dried and evaporated down under reduced pressure. About 9 g of brown substance are obtained which are refluxed with 11.1 ml of 50% aqueous KOH solution in 43 ml of ethanol. After 1 hour the solution is cooled and combined with 40 ml of water. The alcohol is distilled off under reduced pressure. The brown solution is buffered with 40 ml of saturated NH₄Cl solution. The product precipitated is suction filtered and dried. 9.5 g of (3-*tert*-butyl-6-methoxy-phenyl)-thiourea are obtained as a brown powder.

Step 2

9.5 g of (5-*tert*-butyl-2-methoxy-phenyl)-thiourea are dissolved in 130 ml of methanol. 1.9 ml of methyl iodide are added and the mixture is stirred at ambient temperature. After 2 hours the solvent is distilled off under reduced pressure. The oily residue is dissolved in 1.48 ml of ethylenediamine and 100 ml of acetonitrile and the solution is heated to 105°C. After 12 hours the solvent is distilled off under reduced pressure. The residue is dissolved in 20 ml of HCl (1M) and 20 ml of water and extracted with 2x40 ml of ethyl acetate. The organic phases are separated off. The aqueous phase is neutralised with 12 ml of NaOH (1M) and extracted with 2x40 ml of ethyl acetate. The organic phases are separated again. The aqueous phase is made basic with 10

ml of NaOH (1M) and extracted with 2x40 ml of ethyl acetate. All 3 organic phases are combined, dried and evaporated down under reduced pressure. The product is isolated by chromatography (silica gel, eluant: methylene chloride/methanol/ammonia (9/1/1%)).

0.85 g of 3'-*tert*-butyl-6'-methoxy-phen-1'-yl-2-iminoimidazolidine are obtained as a white powder, melting point 172-174°C.

6'-bromo-3'-*tert*-butyl-phen-1'-yl-2-iminoimidazolidine 6

Step 1

0.85 g of 3'-*tert*-butyl-phen-1'-yl-2-iminoimidazolidine are obtained as a white powder from 2.5 g of 3'-*tert*-butylaniline using the same method of synthesis as described for Compound 2 (Steps 1 and 2).

Step 2

0.85 g of 3'-*tert*-butyl-phen-1'-yl-2-iminoimidazolidine are dissolved in 20 ml of methylene chloride and acidified with a few drops of glacial acetic acid. 0.2 ml of bromine are then carefully added dropwise while cooling with an ice bath. The solution is decolorised. It is stirred for 1 hour at 0-5°C. Then the reaction mixture is made alkaline with conc. NH₄OH solution. The organic phase is separated off, dried and evaporated down under reduced pressure. The product is isolated by chromatography (silica gel, eluant: methylene chloride/methanol/ammonia (9/1/1%)). 0.28 g of 6'-bromo-3'-*tert*-butyl-phen-1'-yl-2-iminoimidazolidine are obtained as a white powder, melting point 152-154°C.

The other compounds mentioned may be prepared analogously and/or according to the prior art.

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